Processing Of Formulations

The properties of a drug substance dictate the design of formulation composition and the choice of formulation–processing platform technology.

Most commonly used processing platforms for solid oral dosage form:	Direct Compression (DC)	Powder blends of the drug substance and excipients are compressed on a tablet machine
		No mechanical treatment of the powder apart from a mixing process
	Granulation (wet and dry)	A generic term for particle enlargement
		Powders are formed into permanent aggregates
		Purpose: to improve the flow and compaction properties prior to compression

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Processing Of Formulations

Methods used to achieve the agglomeration

Wet granulation: a liquid is used to aid the agglomeration process

Dry granulation:
no liquid is used

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Processing Of Formulations

Dry Granulation

The primary powder particles are aggregated under high pressure.

Two main processes:

- **Slugging**: A large tablet (known as a "slug") is produced in a heavy-duty tableting press
- **Roller compaction:** Powder is squeezed between two rollers to produce a sheet of material

Intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction.

- Unused fine material may be reworked to avoid waste.

Dry method may be used for

- Drugs that do not compress well after wet granulation, or
- Drugs which are sensitive to moisture.

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Processing Of Formulations

Wet Granulation

- Wet granulation involves the massing of a mix of dry **primary powder particles** using a **granulating fluid.**
  - The fluid contains a solvent which must be volatile so that it is removed by drying, and be nontoxic.
- Typical liquids include

Water	Ethanol	Isopropanol

Either alone or in combination

- The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved **adhesive** (also referred to as a **binder** or **binding agent)** which is used to ensure particle adhesion once the granule is dry.

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Processing Of Formulations

Wet Granulation

Three main methods of producing pharmaceutical granulates

Low-shear granulation | High-shear granulation | Fluid-bed granulation

Low-shear Mixers

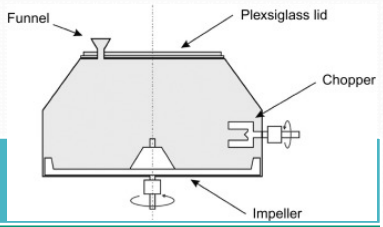
Encompass machines which impart relatively low shear stresses onto the granulate.

Z-blade mixers

Planetary mixers

Processing Of Formulations

Wet Granulation



High-shear Granulators

Closed vessels that normally have two agitators

an impeller which normally covers the diameter of the mixing vessel	a small chopper positioned perpendicular to the impeller.

The powders are dry-mixed using the impeller, and then the granulating fluid is added.

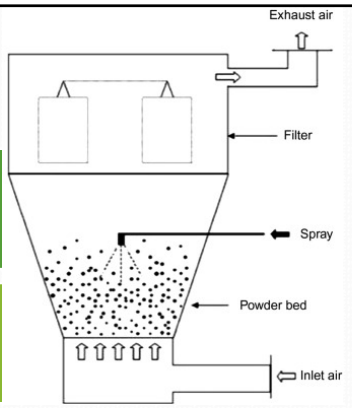
Wet massing takes place using the impeller and the chopper, and granulation is usually completed in a number of minutes.

Processing Of Formulations

Wet Granulation

Fluid-bed Granulation

Involves spraying the dry powder with a granulating fluid inside a fluid-bed drier.



The powder is fluidized in heated air and then sprayed with the granulating fluid.

When all the granulating liquid has been added, the fluidization of the powder continues until the granules are dry.

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Wet Granulation

Influence Of Manufacturing Method On Tableting Performance

- **Drug substance of study:**
  - Paracetamol granulated with hydrolyzed gelatin.
- The main difference in the granules produced by different methods is their final density
  - High-shear mixers produced denser granules than low-shear granulators, which in turn produced denser granules than fluid-bed granulations.
- Disintegration times were greater for tablets produced from the denser granulates.

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Topic 2 - Design of Solid Dosage Formulations

Processing Platforms

Advantages and Disadvantages

Processing Platform	Advantages	Disadvantages
Direct Compression	• Simple, cheap process • Suitable for heat and moisture-labile drugs • Prime particle dissolution	• Generally limited to low-dose compounds • Potential to segregation • Expensive excipients
Dry granulation (Slugging)	• Imparts flowability to formulation • Suitable for heat and moisture-labile drugs	• Dusty process • Not suitable for all compounds • Slow process
Dry granulation (Roller compaction)	• Imparts flowability to formulation • Suitable for heat and moisture-labile drugs	• Slow process • Loss of compactibility for tableting • No hydrophilization of surfaces

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Processing Platforms

Advantages and Disadvantages

Processing Platform	Advantages	Disadvantages
Wet granulation (Aqueous)	• Robust process • Improves flowability • Can reduce elasticity problems • Can improve wettability • Reduces segregation potential	• Expensive • Specialized equipment • Stability concerns for moisture sensitive, thermolabile, and metastable drugs with aqueous granulation
Wet granulation (Nonaqueous)	• Suitable for moisture-sensitive drugs • Vacuum drying techniques can reduce/remove need for heat	• Expensive equipment • Explosion proof • Solvent recovery

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Unit Operations Required for Manufacturing IR Tablet using Various Processing Platforms

Unit Operation	Direct Compression	Dry Granulation	Wet Granulation
Raw materials (weighing and sieving)	✓	✓	✓
Blending	✓	✓	✓
Compaction		✓	
Wet granulation			✓
Wet screening			✓
Drying			✓
Milling		✓	✓
Tablet compression	✓	✓	✓

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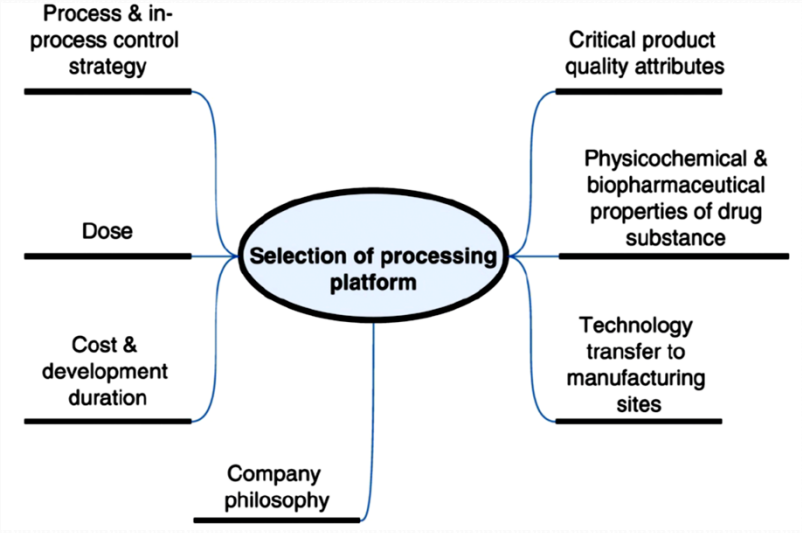
Factors Affecting The Selection Of Processing Platform



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